REMARKS

Claims 1-13 are currently pending and are under examination, claims 14-42 having been withdrawn as directed to an unelected invention.

Claims 1, 3, 4, 8, 10 have been amended. (Withdrawn claims 14, 30, 32, 36, 40 have also been amended so that their scope was similar to that of the active amended claims for possible later rejoinder.)

Responsive to the Office Action, a Substitute Declaration is submitted herewith. That Declaration also has a hand corrected alteration which was initialed and dated by the inventor.

The specification has been amended to correct various informalities (such as inclusion of a statement regarding priority) and typographical errors pointed out by the Examiner. Sections showing sequences expressed in single letter amino acid code have been amended to standard three letter code. Applicants thank the Examiner for his "eagle eye" attention and detection of these errors. It is believed that all such errors or oversights have been adequately addressed.

Specific grounds for objection/rejection and Applicants' amendments and arguments are presented in detail below.

It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully submit that their application is now in condition for allowance.

I. Rejections Under 35 U.S.C. § 112, Second Paragraph

Several grounds for rejection for indefiniteness were asserted. These are briefly indicated below. Claims 3-7, and 10-13 were rejected due to the alleged unclarity of the term "therapeutic label". In claims 4-7, the Action questioned whether the "detectable label" is the same as the "diagnostic label" in claim 3.

Applicants have amended claim 3 to refer to the polypeptide of claim 1:

(1) that is "labeled with a detectable diagnostic label" or

(2) "to which is bound a therapeutically active moiety"

Claim 4 is amended to refer to "the detectably labeled polypeptide of claim 3,}" as suggested by the Examiner.

Claim 10 is amended to recite "the polypeptide of claim 3 to which the therapeutically active moiety is bound directly or indirectly;"

The amended language is supported in the specification and the original claims. It is believed that these amendment place the claims in compliance with § 112, second paragraph, so that the rejection may be withdrawn..

II. Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description

A. The Rejection

Claims 1-13 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is aimed at the language of the broadest claim (claim 1)[1] which recites "a *variant or derivative* of an anti-angiogenic polypeptide having the sequence identified as either SEQ ID NO: 1 or 3." As stated by the Office, to satisfy the written description requirement, the specification must describe the invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. The Action alleges that the specification does not describe the structure (namely, which amino acids) can be altered without affecting the desired function and states that "[t]o be 'in possession' of the claimed invention, the inventor would have had to know the functional consequences of structural alterations." This knowledge is allegedly missing. Given the Office's view that the art has "limited predictability," a skilled person allegedly would not find adequate support in the specification for *variants and derivatives of an anti-angiogenic polypeptide* as recited in claim 1.

B. Applicants' Response

Applicants do not agree with the Office's analysis of the written description requirement as regards their claims and believe that the specification does provide adequate written description for the claims as filed. Applicants believe that the Office is underestimating the relative facility in the art today to predict effects of amino acid substitutions, and, even more powerfully, to screen these

[1] The remaining elected claims, Claims 2-13, were rejected as depending from a rejected base claim.

rapidly in the appropriate biological assays. Thus, it would be almost trivial to predict and then test which variants fall inside or outside the scope of the functional limitations of claim 1.

Notwithstanding this, the Applicants have nevertheless amended claim 1 to limit the variants to conservative substitution variants (supported in the specification) of SEQ ID NO:3 and of SEQ ID NO:1. Based on the disclosed sequences and the relationships among them, Applicants believe that the language in section (c) of claim 1 reciting a two-residue N-terminal addition variant and a seven residue C-terminal replacement variant of SEQ ID NO:1, would comply with the written description requirement of § 112.

Various dependent claims (including withdrawn claims) have been amended to remove reference to "derivatives" and leave in only the "variant" language with its limitations present in amended claim 1.

Based on the foregoing amendments and remarks, it would be proper to withdraw this ground for rejection.

III. Rejections Under § 102

The Office Action rejected various claims as anticipated under § 102(b) and § 102 (a) for the reasons detailed below. In light of the foregoing amendments to the claims and the following discussion, it would be appropriate to withdraw these grounds of rejection.

Legal Test for Novelty:

Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claims". *Jamesbury Corp v. Litton Industrial Products, Inc.*, 225 USPQ 253, 256 (Fed Cir 1985). A §102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it. *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.* 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986). Even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. *In re Donohue*, 226 USPQ 619,621 (Fed. Cir. 1985).

For reasons discussed in detail in the Mazar Declaration submitted herewith, and in the remarks below, Applicants contend that the cited reference do not meet the legal standards set forth above and cannot fairly be said to anticipate the present invention..

A. First Rejection under § 102(b)

Claims 1-3, 8-10, and 13 were rejected as being anticipated by McCrae, K. (WO 00/35407) (hereinafter "McCrae"). Claims 4-7, 11 and 12, all directed to detectably-labeled or therapeutically-conjugated polypeptides, were considered outside the scope of this rejection.

McCrae was said to disclose inhibition of angiogenesis by high molecular weight kininogen domain 3 peptides including those that contain amino acid sequences Asn^{275}-Lys^{282}, Cys^{246}-Cys^{249}, and Leu^{331}-Tyr^{338} (all of which are sequences within HK-D3). The references was cited disclosing that such peptides can inhibit endothelial cell ("EC") proliferation and are said to be useful as anti-angiogenic agents (at page 14, lines 20-28) and as pharmaceutical compositions to inhibit angiogenesis (at page 18, lines 11-16) which composition can be delivered by injection (page 19, line 20-30).

B. Second Rejection under § 102(a)

Similarly, claims 1, and 2 alone were rejected under 35 U.S.C. § 102(a) as being anticipated by Zhang *et al. Can. J. Physiol. Pharmacol. 80*:85-90 (2002) (hereinafter "Zhang"). This document allegedly discloses inhibition of angiogenesis by two-chain high molecular weight kininogen and kininogen derived polypeptides. Specifically, the Action points to disclosure of various activities of two-chain high molecular weight kininogen (which Applicants point out are **distinct from** the claimed polypeptides). These activities include: inhibition of EC cell proliferation (para. 1 of Results section/ Table 1), inhibition of bFGF- and VEFG-induced angiogenesis in the chorioallantoic membrane assay (Fig. 3 and Results section labeled, *HKa and HKa D5 inhibit angiogenesis in vivo*). Zhang also discloses inhibition of EC proliferation and induction of EC cell apoptosis by HK-D3 peptides (Results section, last paragraph and Fig. 5), namely 16mers corresponding to amino acids 267-282 and 275-290 (labeled H3-6 and H3-7, respectively).

C. Applicants' Response to both § 102 Rejections

The Mazar Declaration discusses in detail the HK-D3 peptides which serve as the Office's basis for rejection. McCrae discloses (and actually tests) six peptides each having 16 amino acids, from the D3 domain of HKa. Reference is made elsewhere to shorter 8-mer peptides that are fragments of the 16mers. At the time the specification was prepared, Applicants already knew that some of the data generated using Keith McCrae's peptides was "suspect" as to its interpretation and biological significance. This was discussed in the specification at page 53, paragraph [0215]

(mistakenly referred to as paragraph [0100] in the Declaration, which is reproduced fully in Section 7 of the Declaration. It was clear that these peptides acted through an artifactual mechanism in which they precipitated serum proteins from the medium, became insoluble, and non-specifically killed EC's by sticking to their surfaces and somehow inducing apoptotic death. This is in contrast to the receptor-binding mechanisms by which the polypeptides of the present invention interact with EC's.

The only "real" information about the peptides in McCrae are the results shown in Table 1. It appears that the two peptides that are more biologically active are SEQ ID NO:9 and 10. As discussed in the Mazar Declaration, in Section 6, this was a result of the same artifact. Analysis of the McRae 16-mer peptides, which were also the peptides disclosed in Zhang (H3-6 and H3-7) showed that these were highly insoluble in culture medium under assay conditions for the same reason as the 8mers. Thus, their effects on EC proliferation were not due to a biologic/pharmacologic inhibitory action, but rather to nonspecific, artefactual killing of the cells. This was unavoidable under the assay conditions (see Section 6, page 3, line 7 from top).

The other four peptides shown in McCrae Table 1 were relatively inactive. This is discussed in the Mazar Declaration in Sec. 7. These peptides had activity that was 100-fold lower than those described, exemplified and claimed in the present application. Thus, they did not meet the criterion of claim 1, which has as a limitation an activity that is at least 20% that of native HK-D3. These McRae peptides had activities that were of the order of 1% of native HK-D3.

Importantly, when the two "active" McCrae peptides (also tested in Zhang) were analyzed while in soluble form, for "early" actions on EC's - done in a way that the cells were not at risk for apoptotic death from serum starvation - it was found that the peptides had **no activity.** They did not inhibit MAP kinase activation (an activation that is a prerequisite for EC proliferation) and they did not induce apoptosis through the standard apoptotic pathway. Thus, these peptides had none of the activities attributed to them in the two cited references, and could not be considered to have the characteristics required by Claim 1.

(1) They are not anti-angiogenic peptides - as in soluble form they have low or no activity;

(2) They do not have the length of the polypeptides claimed in amended claim 1 (which is substantially the length of SEQ ID NO:3 or SEQ ID NO:1;they were significantly shorter)

(3) They do not have the requisite at least 20% of the biological activity of native HK-D3.

In view of the amended claims and these stark distinctions therefrom, as emphasized by the Mazar Declaration, it cannot fairly be concluded that McCrae or Zhang anticipate the present claims. Despite their words, these reference simply "had it scientifically wrong." Thus the present claims are novel over these references and the Office is respectfully requested to withdraw these grounds of rejection.

IV. Obviousness Rejections under 35 USC § 103(a)

The Office Action sets forth two combinations of references for rejecting the claims as obvious. For the reasons detailed below, Applicants respectfully submit that it would be appropriate to withdraw these grounds of rejection.

A. First Rejection

Claims 1-13 are rejected as being obvious over McRae (*supra*) in view of Piwnica-Worms, U.S. Patent 6,348,185 (hereinafter "Piwnica")

The Office's description of McRae is given above. The Action notes that, McRae does not disclose a composition wherein the D3 peptide is labeled with a detectable label. This is the subject matter of claims 3 and its dependent claims 4-7 (diagnostics), and 10-13 (therapeutics). Applicants therefore do not understand why this rejection is not limited to claims 4-7 and 10-13.

Piwnica allegedly discloses a composition comprising a peptide, a diagnostic or pharmaceutically active substance, and a linker moiety that links the peptide with a diagnostic or pharmaceutically active substance. The diagnostic substance can be a radionuclide, a relaxivity metal, a fluorochrome, a dye, and an enzyme substrate. The radioactive isotopes disclosed include isotopes of Tc, Ru, In, Ga, Co, Pt, Fe, Os, Ir, W, Re, Cr, Mo, Mn, Rb, Pd, Nb, Cu and Tu (Piwnica, claims 1, 12, and 15). The composition can be administered by injection (column 28, line 27, and Example 10).

From the foregoing, the Office has concluded that one would have been motivated to bind a radionuclide to the anti -angiogenic polypeptide disclosed by McRae to detect and treat disorders related to EC cell proliferation, and angiogenesis, such as metastatic cancer. Therefore, it would have been obvious to label the anti-angiogenic polypeptide of McCrae with a diagnostic or pharmaceutically active substance as disclosed by Piwnica.

B. Second Rejection

Claims 1-13 are rejected as being obvious over Zhang *(supra)* in view of Piwnica *(supra)*.

The Office's description of Zhang is given above. The Action notes that, Zhang does not disclose a composition wherein the HK peptide is labeled with a detectable label or a therapeutically active moiety. Applicants reiterate that they do not understand why this rejection is not limited to claims 4-7 and 10-13.

Piwnica was also discussed above and is combined with Zhang in an identical manner

The Office has concluded that one would have been motivated to bind a radionuclide to the anti -angiogenic polypeptide disclosed by Zhang to detect and treat disorders related to EC cell proliferation, and angiogenesis, such as metastatic cancer. Therefore, it would have been obvious to label the anti-angiogenic polypeptide of McCrae with a diagnostic or pharmaceutically active substance as disclosed by Piwnica.

B. Applicants' Response

(1) The Primary References are Inadequate to Support and Prima Facie Obviousness Rejection

In view of the above discussion of the § 102 rejections, and the conclusion that neither McRae nor Zhang anticipate any of the present claims, these references are inadequate as primary reference to support an obviousness rejection of the remaining (amended) claims that are directed to either diagnostically/detectably labeled D3 polypeptides (claims 4-7) or D3 polypeptides to which is bound a therapeutic moiety (claims 10-13). All these claims depend in one way or another from claim 1.

(2) Applicants further bring to the Examiner's attention a fine, but important, point about the secondary reference used in both asserted combinations under § 103(a). Piwnica describes membrane permeable peptides that target intracellular processes. This is quite distinct from a polypeptide (such as D3) that binds the cell surface via a cell surface receptor. The

characteristics of cell permeable peptides and the chemistry used to attach/conjugate various chemical moieties (whether they be nuclides or otherwise) to them is substantially different from the chemistry used in preparing a cell-surface-targeting labeled/conjugated peptide. Moreover, the process of making a conjugate of any ligand that targets a receptor is specific or selective for that ligand-receptor pair and would not be *prima facie* obvious to someone having ordinary skill in the art from the Piwnica reference alone (or the cited combination).

Therefore, even if the primary references were sufficient, which Applicants contend they are not, the secondary reference would fall short for the reasons provided above. Applicants request the rejection of all the claims under § 103 may properly be withdrawn.

V. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are free of the cited prior art, in compliance with 35 U.S.C. § 112, and therefore in condition for allowance, and respectfully requests early notice of such favorable action.

Examiner Desai is respectfully requested to contact the undersigned at (202) 496-7845 with any questions or comments if they will assist in the understanding this amendment and response.

If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. § 1.136, and any additional fees required under 37 C.F.R. § 1.136 for any necessary extension of time, or any other fees required to complete the filing of this response, may be charged to Deposit Account No. 50-0911. Please credit any overpayment to deposit Account No. 50-0911.

Respectfully submitted,

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By _____

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